EFFECTS OF PROPIONATE ON MECHANICAL AND METABOLIC PERFORMANCE IN RAT HEARTS.

Hakki Bolukoglu, M.D, Stephen H Nellis, Ph.D., A. James Liedtke, M.D., F.A.C.C., Section of Cardiology, University of Wisconsin, Madison, WI

We have prevously shown that propionyl-L-carnitine (PLC) reverses mechanical stunning in myocardial ischemia/reperfusion. Its mechanism of action is unknown. Propionate, a short-chain, odd-number fatty acid, is a potential substrate for oxidation by myocardium. The purpose of this study was to detail and characterize the contributions of propionate as a treatment strategy. Accordingly, six groups of isolated, working rat hearts (n=6-8 per group) were aerobically perfused for 40 min with Krebs-Henseleit media containing 11 mM glucose and varying dosages of propionate [0(placebo),0.1, 0.5, 1.0, 5.0, and 10.0 mM buffered to pH 7.4]. Average aerobic coronary blood flow for all groups was 21.5±0.6 ml/min; average left ventricular peak systolic pressure was 123.7±1.4 mm Hg. There were no significant differences among groups compared with placebo hearts for aortic flow (20.9±0.9 ml/min), heart rate x aortic pressure product (25590±340 bpm x mm Hg), or myocardial oxygen consumption (2.1±0.1 mmol/hr/g dry) although performance tended to decline in the 10 mM group. A clear dose-response relationship was observed in $^{14}CO_2$ production from labeled propionate with a 12 fold increase between the 0.1 and 10 mM propionate groups. Most of the increase occurred at the lower dosages with a relative leveling off at the 1.0, 5.0, and 10.0 mM doses. In separate studies, propionate was also examined as a sole substrate. At 1.0 mM without glucose, propionate per se was unable to support mechanical function over the course of the perfusions but still maintained high rates of oxidation comparable to that noted for the 1.0 mM propionate group with glucose. Tissue glycogen in these hearts was reduced (72±8 µmol/g dry vs 120±9 µmol/g dry in hearts receiving glucose) but not exhausted. Thus, propionate proved a useful adjunctive source of carbon for substrate oxidation in rat hearts. Its contribution to energy metabolism may provide one explanation to understand the benefits of PLC treatments in reperfusion.

Decreased Expression of A Mitochondrial Dehydrogenase Gene in the Uninfarceted Left Ventricle of The Rats

Masashi Arai M.D., Tsugiyasu Kanda M.D., Shoji Okamoto M.D., Shigeru Ohshima M.D., Tadashi Suzuki M.D., Kazuhiko Murata M.D., Akiko Yamamoto Ph.D.

Second Dept. of Internal Medicine & Dept. of Hygiene, Gunma Univ., Gunma, Japan

Acute Myocardial infarction (AMI) induces severe circulatory failure and the uninfarcted myocardium shows marked, compensative hypertrophy. we investigated the expression of proto-oncogenes, genes for contractile proteine, atrial natriouretic peptide (ANP) and mitochondrial dehydrogenase by the Northern blot analyses of the rat hearts. The experimental AMI was made by occlusion of the left coronary artery and mRNAs were isolated from the uninfarcted septum of the LV on 1, 2, 4, 8, 24 hours and 2, 3, 5, 7 days after AMI. There was no induction of nuclear proteins such as c-myc and c-fos oncogenes. In contrast, c-Ha-ras was induced above baseline from 8 hours after AMI. The increase of -actin and ANP mRNA were detected and the switched expression of myosin heavy chain (MHC) gene was confirmed. However, the expression of mitochondrial NADH dehydrogenase submit 1 gene was decreased from 8 hours after AMI and reached to 18% of the sham-operated rats in 5 days.

These results suggest that the decreased expression of NADH dehydrogenase gene in mitochondria is associated with impairment of left vetricluar function and preceding process for the development of compensative hypertrophy after experimental AMI in rats.

GLYCOLYTIC FLUX AND THE TOLERANCE TO ISCHEMIC ARREST IN HYPERTROPHIED-FAILING CANINE HEARTS.

WH Gaasch MD, FACC, MR Zile MD, FACC, CS Apstein MD, FACC. The Medical Center of Central Massachusetts/Memorial, Worcester, MA

The mechanical and biochemical response to an ischemia reperfusion sequence was studied in hypertrophied dog hearts. We studied 15 dogs with LVH (Ao band at 8 weeks, echo-cath at 1 yr); 10 remained compensated (LVH-C): LV fiber shortening and EDP were normal (>35% & <20 mmHg); 5 dogs developed LV pump failure (LVH-F): shortening was <35% & EDP was >20 mmHg. LV/body wt ratio (g/kg) was 4.4±0.3 in 10 controls, 7.7±0.3 in LVH-C, 10±1.1 in LVH-F. The tolerance to 60 min of global ischemia (37°C) followed by 90 min of reflow was studied in isolated blood perfused hearts (isovolumic LV). LV systolic-developed pressure (SP) and EDP were measured at constant LV volume.

Increased sensitivity to ischemia was manifest by ischemic contracture in LVH-F group (EDP increased to 28±7* mmHg at 60 min ischemia); in control & LVH-C groups EDP was unchanged. Tissue ATP (uM/gDW) fell equally in all 3 groups and remained low during reperfusion. *=p<0.05.

	BASELINE			REPERFUSION		
	CONTROL	LVH-C	LVH-F	CONTROL	LVH-C	LVH-F
SP	97±3	104±3	95±4	54±3	49±6	67±8
EDP	10±1	10±1	11±1	13±2	10±1	34±8*
ATP	19±1	17±1	18±2	9±1	9±1	8±2

Coronary flow and MVO_2 were equivalent in the 3 groups at baseline and end reperfusion. All hearts extracted lactate at baseline. However, during early reperfusion lactate washout in the LVH-F group was significantly less than in control and LVH-C groups (2.7±0.6 vs 8.7±2.8* and 8.6±3.8* uM/min/gram DW). Thus, the tolerance to ischemia in LVH-C is similar to normal. Low lactate production in the LVH-F group indicates a reduced capacity to recruit anaerobic glycolysis; this may contribute to ischemic contracture and diastolic dysfunction during reperfusion.

IMPAIRMENT OF CARBOHYDRATE OXIDATION DURING ATRIAL PACING IN PATIENTS WITH SYNDROME X.

Paolo Camici M.D. F.A.C.C., Paolo Marraccini M.D., Roberto Lorenzoni M.D., Roberto Gistri M.D., Giuseppe Buzzigoli, Eleuterio Ferrannini M.D., Antonio L'Abbate M.D. F.A.C.C., Mario Marzilli M.D.
CNR Institute of Clinical Physiology and Istituti di Patologia Medica I e Clinica Medica II, University of Pisa, Italy.

Syndrome X (SX, angina and ST depression on exercise, angiographically normal coronaries, no evidence of spasm) represents, in our experience, about 12% of pts with chest pain and normal coronaries. We studied great cardiac vein (GCV) flow (thermodilution) and transmyocardial substrate handling in 9 SX and 6 normals (N) during atrial pacing (AP). Angina and ST depression occurred in all SX and none of N with AP. Despite comperable HR during AP (167±6 N vs 157±7 bpm SX, p=NS), GCV-flow increased by 126±30% in N and by 46±10% in SX (p<0.05). LV ejection fraction (ventriculography) during AP was comparable (66±2% N vs 71±2% SX, p=NS). The extraction fraction of lactate during AP was similar (28±5% N vs 27±4% SX, p=NS) and in no instance was lactate release observed. During AP FFA upteke was comparable (13.8±2.9 N vs 10.6±2.3 µmol/min SX, p=NS) and lipid oxidation (indirect calorimetry) was higher in SX although the difference fell short of statistical significance (9.1±6.1 N vs 17.9±8.9 µmol/min SX, p=NS). By contrast, despite similar carbohydrate (glucose + lactate + pyruvate + alanine) upteke during AP (25.1±8.8 N vs 22.7±2.3 µmol/min SX, p=NS), carbohydrate oxidation was 59.6±23.9 µmol/min in N while it was not different from zero in SX.

In conclusion: a) during AP pts with SX have angina, ST depression and a reduced GCV-flow increment; b) however, they have good LV function, normal FFA and lactate metabolism but an impaired oxidation of carbohydrate fuel.